Attributable Mortality of Ventilator-Associated Pneumonia
A Reappraisal Using Causal Analysis

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Rationale: Measuring the attributable mortality of ventilator-associated pneumonia (VAP) is challenging and prone to different forms of bias. Studies addressing this issue have produced variable and controversial results.

Objectives: We estimate the attributable mortality of VAP in a large multicenter cohort using statistical methods from the field of causal inference.

Methods: Patients (n = 4,479) from the longitudinal prospective (1997–2008) French multicenter Outcomerea database were included if they stayed in the intensive care unit (ICU) for at least 2 days and received mechanical ventilation (MV) within 48 hours after ICU admission. A competing risk survival analysis, treating ICU discharge as a competing risk for ICU mortality, was conducted using a marginal structural modeling approach to adjust for time-varying confounding by disease severity.

Measurements and Main Results: Six hundred eighty-five (15.3%) patients acquired at least one episode of VAP. We estimated that 4.4% (95% confidence interval, 1.6–7.0%) of the deaths in the ICU on Day 30 and 5.9% (95% confidence interval, 2.5–9.1%) on Day 60 are attributable to VAP. With an observed ICU mortality of 23.3% on Day 30 and 25.6% on Day 60, this corresponds to an ICU mortality attributable to VAP of about 1% on Day 30 and 1.5% on Day 60.

Conclusions: Our study on the attributable mortality of VAP is the first that simultaneously accounts for the time of acquiring VAP, informative loss to follow-up after ICU discharge, and the existence of complex feedback relations between VAP and the evolution of disease severity. In contrast to the majority of previous reports, we detected a relatively limited attributable ICU mortality of VAP.

Keywords: ventilator-associated pneumonia; attributable mortality; causal inference; severity of illness

Ventilator-associated pneumonia (VAP) is the leading nosocomial infection in mechanically ventilated, critically ill patients

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Scientific Knowledge on the Subject

There is much controversy regarding the attributable mortality of ventilator-associated pneumonia (VAP). To the best of our knowledge, current studies have completely ignored confounding by time-dependent severity-of-illness indicators. It has therefore been recently emphasized that methods with more methodological rigor are required to estimate the attributable mortality.

What This Study Adds to the Field

This study provides one of the most accurate assessments of the attributable mortality of VAP published so far because it combines the strengths of novel statistical methodology with a large high-quality multicenter database, which incorporated the evolution in severity of illness from intensive care unit (ICU) admission until ICU discharge or death. In contrast to the majority of previous reports, we detected a relatively limited attributable ICU-mortality.

and is commonly considered as a partly preventable disease with a high risk for adverse outcome (1, 2). Assessment of the attributable mortality of VAP nevertheless remains challenging (3–5). The large variability (1, 5, 6) in estimated excess risk of death from VAP (between 0 and 70%) has been primarily explained by differences in the patient population under study (case-mix) as well as by the absence of a reference standard diagnosis for VAP, which is usually replaced by a clinical probability coupled with quantitative microbiological data to improve specificity (7, 8). In our opinion, the use of various definitions of excess risk also contributes to that variation, as well as methodological shortcomings on the level of the data analysis, which may lead to over- or underestimation of the mortality attributable to VAP. As investigators have to rely on observational data alone, careful adjustment for confounding by severity of illness is required to disentangle the complex relationship between VAP and mortality. This is because VAP is essentially a complication of underlying critical illness (9, 10) and because patients who acquire VAP tend to be more severely ill than patients who do not.

To obtain unbiased estimates of the attributable mortality of nosocomial infections, methods should account for obvious findings: (1) patients need to survive long enough to acquire infection; (2) patients who acquire infection tend to be more...
severely ill in the course of their critical illness and not only on admission; (3) there is a dynamic interplay between VAP and the patients’ severity of illness, clinical characteristics, and treatment over time; and (4) patients who get discharged from the intensive care unit (ICU) and whose survival time is therefore censored tend to be in different health conditions as compared with patients staying at the ICU.

This study is the first to estimate the population-attributable risk of ICU mortality by VAP in a large-sized, high-quality, multicenter database (6), while overcoming all of the aforementioned obstacles. This is achieved through the use of statistical techniques from the field of causal inference (11, 12). Similar causal analyses have proved successful in the reanalysis of the Women’s Health Initiative Study (13, 14) and of epidemiologic studies of AIDS therapies (15), wherein standard statistical methods contradicted results from the analysis of randomized trials. In this article, we adopted the same modeling approach as in these studies but extended with further refinements that carefully take into account that censoring of the survival time due to discharge from the ICU contains information on the actual survival time (12). Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

Study Population and Data Collection

The analysis was based on all records in the longitudinal (1997–2008) French multicenter Outcomerea database from patients who stayed in the ICU for at least 2 days and received mechanical ventilation (MV) within 48 hours after ICU admission. In accordance with previous reports (6), VAP was defined as persistent pulmonary infiltrates on chest radiographs combined with purulent tracheal secretions, and/or body temperature greater than or equal to 38.5°C or less than or equal to 36.5°C, and/or peripheral blood leukocyte count greater than or equal to 10 × 10^9/L or less than or equal to 4 × 10^9/L. A definitive diagnosis of VAP required microbiological confirmation by quantitative culture from a protected specimen brush (> 10^9 cfu/ml), plugged telescopic catheter specimen (> 10^8 cfu/ml), bronchoalveolar lavage (BAL) fluid specimen (> 10^5 cfu/ml), or endotracheal aspirate (> 10^2 cfu/ml). The effect of the first acquired microbiological proven VAP was modeled.

Data were collected as described previously (6). In short, the participating ICUs provided a random sample of at least 50 ICU stays of >24 hours per patient; per case, data entered in the case report form included admission characteristics as well as events and scores after ICU admission that were recorded on a daily basis. Measured characteristics on admission consisted of demographic data, admission diagnosis and admission category, chronic illness and comorbidity (using the Knaus definition and including the McCabe score), clinical findings, and laboratory investigations. On admission and subsequently on a daily basis, the following scores were calculated: Simplified Acute Physiology Score (SAPS) II (17), Sequential Organ Failure Assessment (SOFA) (18), and Logistic Organ Dysfunction score (17). In addition, data on daily interventions and treatments were collected: antibiotic treatment, enteral feeding, corticosteroids greater than 0.5 mg/kg, invasive or noninvasive mechanical ventilation, vasopressor use, hemodialysis, placement and presence of invasive devices (arterial catheter, central venous catheter, Swan-Ganz catheter, and Foley catheter), tracheostomy, and do-not-resuscitate (DNR) orders. Throughout the article we refer to the above-described variables as severity of illness indicators. Antimicrobial treatment was considered immediately appropriate if at the day of microbiological sampling the patient received at least one antibiotic to which the recovered pathogen(s) was susceptible in vitro.

Statistical Analysis

A key challenge for statistical analysis is that patients with and without VAP are inherently different in severity of illness (before the acquisition of VAP) so that mortality differences between these groups cannot be fully attributed to VAP. When differences in disease severity between these groups are entirely explainable in terms of patient characteristics measured on ICU admission, then adjustment is possible by including these as covariates in the analysis. This is no longer sufficient when evolution in disease severity also contributes to the difference between these patient populations. In that case, standard regression adjustment for the evolution in severity of illness eliminates the effects of early VAP that are mediated through severity of illness and in addition induces a so-called collider-stratification bias (11, 15, 31).

In view of this, we opted for a marginal structural modeling approach (11, 12, 19), which enables assessment of what the ICU mortality would have been if all patients had remained VAP-free or, alternatively, had acquired VAP on a specific day. Because information on this is lacking for patients who acquired VAP, the observed data for VAP-free patients is reweighted to predict what the ICU mortality status would have been for patients with VAP, had VAP been prevented for them. For instance, let us suppose that a VAP-free patient, based on his evolution in disease severity, has a one in three chance of not acquiring VAP. Then for every such patient, one expects to find two patients in the population who experienced a similar evolution in severity of illness but who did acquire VAP. To estimate what the ICU mortality would have been if all patients had remained VAP-free, the data for that VAP-free patient will therefore be counted three times: one time to represent himself and two additional times to represent those like patients who did acquire infection. By repeating this for all VAP-free patients, one can thus reconstruct how the data on ICU mortality status would have looked, had VAP been prevented for all.

The intuitive principle underlying this estimation procedure is illustrated by numerical example in Reference 11. The details and validity of the approach in this context are reported in Reference 12; we here outline the main steps.

In a first step, we fitted a logistic regression model for the daily probability of acquiring VAP. Because mechanical ventilation could be stopped or restarted on each day, this model includes the patient’s time-dependent ventilation status. The obtained probabilities then served to generate a daily patient-specific weighing factor, which was defined as the reciprocal of the probability of the patient having his observed VAP status and previous history by that day (12). Because severity-of-illness indicators measured on a given day may have been influenced by infection acquired on that day, the model for VAP included only lagged values from the day before. For the SOFA score and antibiotic use we adjusted for lagged values 3 days (72 h) before to recognize that the SOFA score and the antibiotic use within 48 hours before the onset of VAP are possible surrogate markers for an infection that was incubating and that may therefore be affected by VAP on the given day. All analyses were additionally adjusted for the ICU center and the admission year.

In the second stage of the analysis, we accounted for informative censoring of the survival time through a competing risk analysis (20, 21) whereby we considered discharge from the ICU as a competing risk for ICU mortality (22). Our primary focus was on 60-day ICU mortality, because many VAP deaths occur after the first 30 days of ICU stay and because the analysis of more distal endpoints, such as overall hospital mortality, requires a more stringent confounding adjustment. Using the proposed weights, we evaluated hazard regression models, involving the so-called subdistribution hazard, which measures at each time the instantaneous risk of ICU death at that time among patients who did not die within the ICU before that time (12). From these models, we inferred the impact of acquiring VAP in the ICU on the cumulative incidence function of ICU death, which is the probability of dying within the ICU before a given time, as a function of time. This was then used to estimate the attributable mortality of VAP as the population-attributable fraction (23) of ICU mortality related to infection. On each day, this was calculated as the difference between the observed ICU mortality and the ICU mortality that would have been observed for the same population if VAP were prevented for all, divided by the observed ICU mortality. It can be interpreted as the percentage of the observed ICU deaths that could be avoided by preventing VAP, or, as the percentage of the observed ICU patients who died because of VAP (24).
In total 868 microorganisms were isolated from the 685 ventilator-associated pneumonia episodes.

All models were built using a stepwise model selection approach at the 5% significance level using SAS 9.2 (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptives

A total of 4,479 patients from the Outcomerea database fulfilled the inclusion criteria, 685 (15.3%) of whom developed pneumonia within 30 days after ICU admission. Forty-one patients (5.9%) were diagnosed with pneumonia more than 48 hours after the inclusion criteria, 685 (15.3%) of whom developed pneumonia within 30 days after ICU admission. Forty-one patients (5.9%) were diagnosed with pneumonia more than 48 hours after

<p>|TABLE 1. OVERVIEW OF THE MAIN MICROORGANISMS CAUSING VENTILATOR-ASSOCIATED PNEUMONIA|
|-----------------------------|-----------|</p>
<table>
<thead>
<tr>
<th>Microorganism</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive</td>
<td>244 (28.1)</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>45 (5.2)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>868</td>
</tr>
<tr>
<td>Methicillin susceptible</td>
<td>84 (9.7)</td>
</tr>
<tr>
<td>Methicillin resistant</td>
<td>49 (5.6)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>32 (3.7)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Streptococcus, other</td>
<td>27 (3.1)</td>
</tr>
<tr>
<td>Gram negative</td>
<td>554 (63.8)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>63 (7.3)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>66 (7.6)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>38 (4.4)</td>
</tr>
<tr>
<td>Enterobacter sp.</td>
<td>37 (4.3)</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>21 (2.4)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>14 (1.6)</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>13 (1.5)</td>
</tr>
<tr>
<td>Nonfermenting pathogens</td>
<td>70 (8.1)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>155 (17.9)</td>
</tr>
<tr>
<td>Wild type</td>
<td>72 (8.3)</td>
</tr>
<tr>
<td>Resistance mechanism</td>
<td>24 (8.2)</td>
</tr>
<tr>
<td>Acinetobacter sp.</td>
<td>35 (4.0)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>45 (5.2)</td>
</tr>
</tbody>
</table>

In total 868 microorganisms were isolated from the 685 ventilator-associated pneumonia episodes.

Risk of Acquiring VAP

The change in hazard of acquiring VAP with time was modeled in a flexible way allowing for differences in evolution depending on the patient’s sex ($P = 0.01$), underlying severity of illness (as measured by the SOFA score on ICU admission) ($P = 0.02$), and on antibiotic treatment on admission ($P < 0.001$). Mechanical ventilation ($P < 0.001$) and enteral feeding the day before the possible occurrence of VAP were associated with an increased risk of acquiring VAP. The magnitude of the effect of enteral feeding increased with higher SOFA scores 72 hours before the possible occurrence of VAP ($P = 0.02$). The impact of SOFA on the risk of acquiring VAP followed opposite directions depending on the value at admission ($P = 0.03$), with an increasing risk for patients with an initial value below 10 and a decreasing risk for patients with a higher initial SOFA. A DNR order ($P = 0.02$) and antibiotic treatment on admission and 72 hours before the occurrence of VAP ($P < 0.001$) were associated with a lower risk of VAP. Finally, patients with a urinary tract ($P = 0.04$) and catheter-related infection ($P < 0.001$) 24 hours before the possible occurrence of VAP were more vulnerable to acquire VAP unless the urinary tract infection was acquired more than 6 days ($P = 0.02$) before the occurrence of VAP. (Note that these results should not be causally interpreted, as they are merely used to create a statistical population in which VAP on each day is independent of measured daily indicators of disease severity, so as to enable an unbiased assessment of the attributable ICU mortality of VAP.)

Attributable ICU Mortality due to VAP

From the marginal structural modeling analysis we found that the (subdistribution) hazard of ICU death increased 2.3% per additional day since the onset of VAP (hazard ratio [HR], 1.02; 95% confidence interval [CI], 1.01–1.034; $P < 0.001$). Corresponding increases in HRs of 2.0% (HR, 1.02; 95% CI,
1.007–1.034; \( P = 0.003 \)) and 2.7\% (HR, 1.027; 95\% CI, 1.017–1.047; \( P = 0.001 \)) were observed for appropriately versus inappropriately treated VAP, respectively. The effect of VAP on ICU mortality further depended on the patient’s severity of illness on ICU admission (\( P = 0.01 \)). Table 3 gives an overview of the HRs of ICU death per additional day since infection. The effect of VAP was the largest for patients with intermediate (28–40) SAPS II scores and attenuated in patients with high (>65) or low (<20) SAPS II scores.

Figure 1 displays the effect of VAP on ICU mortality over time. On Day 30 and Day 60, the population-attributable fraction of ICU mortality due to VAP (Figure 2) equals 4.4\% (95\% CI, 1.6–7.0\%) and 5.9\% (95\% CI, 2.5–9.1\%), respectively. For instance, on Day 30 this means that if one were able to prevent VAP for all patients in the ICU, 4.4\% (95\% CI, 1.6–7.0\%) of the observed ICU deaths within the first 30 days after ICU admission could be avoided.

**DISCUSSION**

We estimated that 4.4\% (95\% CI, 1.6–7.0\%) of the deaths in the ICU on Day 30 and 5.9\% (95\% CI, 2.5–9.1\%) on Day 60 could be attributed to VAP, after careful adjustment for time-varying disease severity through the use of a marginal structural modeling analysis and for ICU discharge as a competing risk for mortality through the use of competing risk analysis. With an observed ICU mortality of 23.3\% on Day 30 and 25.6\% on Day 60, this corresponds to an ICU mortality attributable to VAP of about 1\% on Day 30 and 1.5\% on Day 60. As in previous studies on VAP and hospital-acquired bloodstream infections (6, 25, 26), our results also indicate that patients who are more critically ill on admission (higher range of SAPS II) do not experience a major attributable (or additional) effect of VAP compared with those with an intermediate SAPS II score (28–40). The likely explanation for this phenomenon is that the risk of death in patients with established severe organ failure is less modifiable by subsequent treatment or by intercurrent complications. On the other hand, the lower attributable mortality of VAP in patients in the lower range of SAPS II could be biologically explained by better preservation of host defense mechanisms in these patients (27) and by a larger window of opportunity to alter natural history of the infection by appropriate treatment.

The problem of attributable mortality of VAP has already generated a considerable literature. However, only a minority of the studies published thus far performed multivariate analysis to control the association between VAP and mortality for confounding by severity of illness (4, 5). Furthermore, although a number of authors (6, 28–30) have previously made progress in terms of estimating the attributable effect of VAP by carefully acknowledging the time at which infection is acquired in their analysis, to the best of our knowledge, all previous reports ignored confounding by the evolution of disease severity over time. The challenge is how to incorporate the existence of complex feedback relations between VAP, underlying critical illness, and evolving organ failure over time (12, 31). By using standard statistical regression methods to control for severity-of-illness indicators, one introduces a so-called collider-stratification bias (11, 32). Even when controlling only for severity of illness before infection, such bias results because the severity of illness on a given day is influenced by (the absence of) infection on the previous days. Therefore, whereas the wide range of estimated

**Table 3. Hazard Ratios of Intensive Care Unit Death per Additional Day Since Infection Calculated for Patients with Different SAPS II Scores on Admission (Different Percentiles)**

<table>
<thead>
<tr>
<th>SAPS II on Admission</th>
<th>Hazard Ratio of ICU Death per Additional Day Since Infection (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (5%)</td>
<td>1.023 (0.980–1.068)</td>
<td>0.31</td>
</tr>
<tr>
<td>20 (10%)</td>
<td>1.030 (0.997–1.063)</td>
<td>0.07</td>
</tr>
<tr>
<td>28 (25%)</td>
<td>1.037 (1.018–1.056)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40 (50%)</td>
<td>1.038 (1.025–1.052)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>53 (75%)</td>
<td>1.027 (1.013–1.041)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65 (90%)</td>
<td>1.00 (0.989–1.022)</td>
<td>0.49</td>
</tr>
<tr>
<td>73 (95%)</td>
<td>0.990 (0.960–1.010)</td>
<td>0.28</td>
</tr>
<tr>
<td>Overall</td>
<td>1.023 (1.011–1.034)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score II.*

Figure 1. The observed cumulative intensive care unit (ICU) mortality together with the ICU mortality as it would have been observed for the same population if ventilator-associated pneumonia (VAP) were prevented for all.
attributable mortality may reflect true differences resulting from case mix and appropriateness of treatment, in our opinion it additionally reflects incorrect and incomplete adjustment for the condition (and hence the inherent risk of death) of the patient at the very time of developing VAP. The continuous monitoring of vital and biochemical parameters of patients during their stay at the ICU offers the potential to correct for longitudinal information on the patient’s health condition evolving over the duration of their critical illness. To incorporate this huge set of data in a meaningful way, a close collaboration between clinicians with a good bedside experience in the treatment of these patients and statisticians who are able to develop and/or use more advanced complex statistical techniques that appropriately account for the aforementioned biases is mandatory. Our study is the first to address all of them via the use of techniques from the field of causal inference.

In contrast to the majority of previous reports (see Reference 4 for a systematic review), we obtained a relatively mild attributable ICU mortality of VAP. A comparison is nevertheless difficult to make because previous studies often focus on alternative risk measures, such as relative risks, odds ratios, or HRs. Our focus on the population-attributable fraction has the advantage that it translates into daily estimates of attributable mortality with a clear medical interpretation because they express the percentage of observed ICU deaths by that day whose death was a consequence of VAP. Similarly, they reflect the percentage of ICU deaths by that day that could be avoided if VAP could be completely prevented.

Because in the popular press nosocomial infection, including VAP, is increasingly depicted as a preventable disease leading to avoidable death, thus having legal implications, an accurate measure of the attributable mortality of VAP has importance beyond its academic interest. However, it would be erroneous to use our result as a justification to neglect measures to prevent VAP or to minimize the importance of VAP diagnosis and treatment. As in other studies, the attributable mortality of VAP does not reflect the natural history of the disease itself but the effect of disease modified by therapy, including advanced organ support in addition to antimicrobial therapy. Because modern intensive care can support or partially replace vital functions for prolonged periods of time and for high levels of organ dysfunction, the relationship between VAP and overall mortality is mitigated or obscured. This is congruent to daily clinical practice, in which a direct relationship between occurrence of VAP and death is rarely observed as long as decisions to forego life-sustaining therapy are not taken. Furthermore, similarly to all previous studies, the impact of VAP is measured relative to the absence of VAP but not to the absence of nosocomial infection altogether, such as urinary tract or catheter-related infections. Finally, our study did not address attributable morbidity of VAP, such as expressed by ICU length-of-stay.

Although our study took into account as much information as possible and used advanced statistical methodology to correct for various biases, several limitations must be acknowledged. First, like all analyses of observational studies, the validity of our analysis relies on the assumption that all relevant confounders have been taken into account. Without confounding adjustment, one can only learn about the association between VAP and mortality. This association is of little account when no causal interpretation can be given, because the relevant scientific question is a causal one: do patients die from (i.e., due to) or with infection? Second, our analysis did not adjust for measurement error in the patient’s VAP status. Measurement error of the timing of VAP onset may arise by the process of disease incubation being gradual. This could affect our analysis, which is explicit that cause must precede effect. In view of this, we used lagged values measured from the day before to predict VAP on each day (and of 3 days before in the case of the SOFA score and antibiotic treatment). It is unclear whether this adjustment sufficiently corrected for an incubation effect, although a sensitivity analysis (not shown) revealed little impact of the chosen lag time. Measurement error may also arise when the VAP status is not systematically recorded for patients with a DNR code (e.g., by refraining from microbiological sampling or chest X-ray). Third, unlike others, we do not provide subgroup analyses. This is because restriction of the analysis to subgroups that are defined on the basis of time-dependent health characteristics may introduce a collider-stratification bias (31, 32). For instance, the analysis of subgroups defined by the type of pathogen is challenging because the type of pathogen can be related with time-dependent health characteristics. Indeed, it is well known that P. aeruginosa often persists in cultures of tracheotomized patients. As such, this pathogen may in a certain number of patients be a surrogate marker of tracheotomy, which by itself is a surrogate marker of severe critical illness polyneuropathy. Further methodological development is needed to enable the assessment of effect modification by time-dependent measures of disease severity. Finally, one should also note that, whereas all patients involved in this analysis were ventilated for more than 48 hours, 5.9% of the 685 patients who acquired a VAP were already extubated more than 48 hours. This small percentage of patients may not be technically classified as patients with VAP. A reanalysis in which these patients are reclassified as patients without VAP gave similar results: that 3.7% (95% CI, 0.5–6.8%) of the deaths in the ICU on Day 30 and 5.2% (95% CI, 1.6–8.6%) on Day 60 are attributable to VAP.

In conclusion, this study on the attributable mortality of VAP is the first that appropriately accounts for the timing of acquiring VAP, for the existence of complex feedback relations between VAP and disease severity, and for informative loss to follow-up after ICU discharge. In contrast to the majority of previous reports, we detected a relatively limited attributable ICU mortality.
Author Disclosure
M.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.-F.T.'s institution has received board membership fees from 3M; consultancy fees from Astellas; grants from 3M, Astellas, Ethicon, Pfizer, and Merck; and lecture fees from Astellas and Philips. He has received board membership fees and lecture fees from Merck. S.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.G.-O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.A.'s institution has received board membership fees from Pfizer and Gilead; he has received consultancy fees and lecture fees from Pfizer and Gilead. D.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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